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ORODISPERSIBLE PHARMACEUTICAL COMPOSITION COMPROSING MITIGLINIDE
[Composition Phatmaceutique Orodispersible de Mitiglinide]

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TITLE	(54):	ORODISPERSIBLE PHARMACEUTICAL COMPOSITION COMPROSING MITIGLINIDE
FOREIGN TITLE	[54A]:	Composition Phatmaceutique Orodispersible de Mitiglinide

The object of this invention is a solid orodispersible pharmaceutical form of mitiglinide or the /1*
pharmaceutically acceptable salts thereof for the oral administration without a simultaneous glass of water and without swallowing problems.

Mitiglinide, or (2*S*)-2-benzyl-4-[(3aR,7aS)-octahydro-2H-isoindol-2-yl]-4-oxobutanoic acid, is a powerful insulin secretor which is useful in the treatment of type 2 diabetes.

Mitiglinide can be administered orally as tablets to be swallowed with one-half glass of water.

In particular, mitiglinide is presented in the form of a dihydrated calcium salt or calcium bis-{(2S)-2-benzyl-4-[(3aR, 7aS)-octahydro-2H-isoindol-2-yl]-4-oxobutanoate}dihydrate.

The doses of dihydrated calcium salt of mitiglinide used to obtain the desired therapeutic effect are generally 5-40 mg per individual dose, three to four times per day, in the form of immediate-release tablets.

Many people have difficulty swallowing conventional tablets, which are often quite large. Problems related to ingestion of drugs (choking or asphyxiation by obstruction of the throat) result in poor compliance with the dosage or even discontinuation of treatment.

The pharmaceutical compositions of this invention not only remedy the known disadvantages of the tablet form to be swallowed, but also offer a superior medical service, which improves patients' quality of life.

The advantage of the orodispersible pharmaceutical composition of mitiglinide is that high plasma /2
levels of the active ingredient can be obtained rapidly.

The orodispersible pharmaceutical composition according to the invention has the particular characteristic of requiring neither water nor chewing when it is taken. It disintegrates rapidly in the mouth, preferably in less than three minutes, and more preferably in less than one minute.

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* [The numbers in the right margin indicate pagination of the original text.]

A number of fast-dissolving forms are described in the prior art. In general, the technologies described previously have in common the use of a disintegrating agent such as Kollidon® CL (crosslinked polyvinylpyrrolidone), EXPLOTAB® (carboxymethylated starch), or AC DISOL® (crosslinked sodium carboxymethylcellulose).

This disintegrating agent is essential in the formulation of orodispersible tablets, and should be used together with a direct compression excipient. The difficulties encountered in the manufacture of these tablets is that it is extremely difficult to obtain tablets with constant physical characteristics that are reproducible and compatible with the standard constraints of handling tablets.

In fact, the mixtures traditionally used lead to tablets which are extremely hard and completely unsuitable for rapid disintegration in the oral cavity.

Other orodispersible forms can be made by using lyophilization, which results in highly porous solid forms called "oral lyophilizates." These forms require the use of a highly specific industrial process that is complicated and time-consuming, and results in a high-priced product.

These disadvantages are remedied by the present invention. It concerns a solid orodispersible form of mitiglinide containing a simple excipient of natural origin that permits complete disintegration; it has a neutral taste and a pleasant texture. This excipient acts as both a binder and a disintegration agent. It /3
permits a simple formulation of mitiglinide with excellent aptitude for direct compression, resulting in tablets of low friability and with a hardness compatible with the standard manipulation techniques.

In particular, the invention concerns a solid orodispersible pharmaceutical composition of mitiglinide or a pharmaceutically acceptable salt thereof, characterized in that it contains:

-mitiglinide or a pharmaceutically acceptable salt thereof

-and granules consisting of co-dried lactose and starch.

Preferably, the mitiglinide is present in the form of dihydrated calcium salt.

The composition according to the invention may also contain, for reasons of manufacture, one or more lubricants and a flow agent as well as flavors, dyes, and sweeteners that are traditionally used.

To improve the masking of the bitter taste of mitiglinide, the latter may be combined with excipients such as cyclodextrins or coated with excipients by using technology known to a person skilled in the art, such as coating in a fluidized bed, spraying, coacervation, prilling, and spray congealing.

Another object of the invention is the use of granules made of co-dried lactose and starch to prepare solid orodispersible pharmaceutical compositions of mitiglinide.

The term "orodispersible" means solid pharmaceutical compositions that disintegrate in the oral cavity in less than 3 minutes, preferably in less than one minute.

Said granules included in the solid pharmaceutical compositions according to the invention /4
correspond to the compositions described in the patent application EP 00/402159.8. These granules are characterized by a spherical structure and advantageous compressibility, and are sold under the name of STARLAC®.

The disintegrating properties of said granules are known for tablets placed in large volumes of liquid under agitation. It is particularly surprising that such granules used for the manufacture of orodispersible forms can yield particularly satisfactory results in terms of disintegration in the mouth, for two reasons.

The first reason is based on the observation that the least water-soluble excipients are the most appropriate for the formation of orodispersible tablets (solubilization, which increases the viscosity of the water, is a hindrance to its penetration into the tablets). These granules comprise a substantial fraction of highly water-soluble lactose. In addition, the starch included in said granules is not a "super disintegrating" agent as used and described in the orodispersible forms of the prior art.

The second reason is based on the observation that the disintegration properties of an excipient (used in a tablet) evaluated in water by the conventional method cannot be extrapolated to the behavior of the

same tablet in vivo, in saliva. In fact, the disintegration rates in water are measured (according to the European Pharmacopeia) in enough water that saturation will not be reached at the end of solubilization, whereas in vivo, because of the small volume of saliva, the excipients are at saturation. In addition, the agitation the tablets undergo in the usual test does not reflect decomposition in the mouth. Therefore, the Applicant has noted in comparative tests that some excipients known to be good disintegrating agents were not adapted to the preparation of orodispersible forms. Conversely, some excipients that disintegrate moderately well in water may present advantageous properties in vivo.

Accordingly, the Applicant has found that these granules, surprisingly, conferred on the tablets an excellent ability to disintegrate in the mouth, and this applies to a wide range of tablet hardness, while /5
preserving a low friability, which is particularly remarkable. In fact, most of the orodispersible forms of the prior art that disintegrate rapidly in the mouth are highly friable, which results in the need for specific packaging and the risk that the tablet will disintegrate when it is handled and removed from its container.

It is particularly remarkable that the criteria of orodispersibility and low friability as mentioned above are respected for a wide range of tablet hardness, specifically for tablets with a hardness between 15 and 30 Newtons.

The pharmaceutical compositions according to the invention are preferably characterized in that they contain, with respect to the total weight of the tablet:

-2.5-20 wt% of mitiglinide or a pharmaceutically acceptable salt thereof,

-75-95 wt% of STARLAC®.

They may contain from 0.1-3 wt% of lubricants such as stearyl sodium fumarate or magnesium stearate, preferably from 0.5-1.5%, and from 0.1-3 wt% of a flow agent such as colloidal silica, preferably 0.5-1.5%.

The following examples illustrate the invention but do not limit it in any way:

Orodispersible tablets of mitiglinide.

EXAMPLE 1:

Formulation: 100-mg finished tablet

Constituents	Quantity (mg)
Mitiglinide, dihydrated calcium salt	10
Starlac®	88
Magnesium stearate	1.5
Anhydrous colloidal silica	0.5

EXAMPLE 2: /6

Formulation: 400-mg finished tablet

Constituents	Quantity (mg)
Mitiglinide, dihydrated calcium salt	40
Starlac®	352
Stearyl sodium fumarate	6
Anhydrous colloidal silica	2

The tablets are prepared by mixing the constituents, followed by direct compression. The hardness of the tablets of Examples 1 and 2 is about 20 Newtons.

To evaluate the disintegration time in the mouth, the orodispersible tablets of mitiglinide described in Examples 1 and 2 were placed in the mouth. In these tests, it was shown that for each of the formulations tested, the disintegration time in the mouth was less than 1 minute.

Claims /7

1. Solid orodispersible pharmaceutical composition of mitiglinide or pharmaceutically acceptable salts thereof, characterized in that it includes:

-mitiglinide, or a pharmaceutically acceptable salt thereof

-granules consisting of co-dried lactose and starch.

2. Pharmaceutical composition according to Claim 1, characterized in that it includes, with respect to the total weight of the composition:

-2.5-20 wt% of mitiglinide or a pharmaceutically acceptable salt thereof,

-75-95 wt% granules consisting of co-dried lactose and starch.

3. Pharmaceutical composition according to Claim 2, characterized in that it includes 5-10 wt% mitiglinide or a pharmaceutically acceptable salt thereof.

4. Pharmaceutical composition according to Claim 1, characterized in that it also includes one or more lubricants and a flow agent.

5. Pharmaceutical composition according to Claim 1, characterized in that it is presented in tablet form.

6. Tablet according to Claim 5, characterized in that it is obtained by direct compression.

7. Tablet according to Claim 6, characterized in that its hardness is between 15 and 50 Newtons.

8. Tablet according to Claim 7, characterized in that its hardness is equal to approximately 20 Newtons.

9. Use of granules consisting of co-dried lactose and starch to manufacture orodispersible solid compositions of mitiglinide that disintegrate in the mouth in less than three minutes, and preferably in less than one minute. /8

10. Solid, orodispersible pharmaceutical composition of mitiglinide or a pharmaceutically acceptable salt thereof, according to Claim 1, useful for treatment of diabetes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/FR 03/00196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4035 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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